PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3:
A61K 31/165

A1

(11) International Publication Number: WO 81/02975

(43) International Publication Date: 29 October 1981 (29.10.81)

(21) International Application Number: PCT/US81/00520

(22) International Filing Date: 20 April 1981 (20.04.81)

(31) Priority Application Number: 142,279

(32) Priority Date: 21 April 1980 (21.04.80)

(33) Priority Country: US

(71) Applicant: UNIVERSITY OF SOUTHERN CALIFORNIA [US/US]; University Park, Los Angeles, CA 90007 (US).

(72) Inventor: SWARBRICK, James; 895 Old Mill Road, Pasadena, CA 91108 (US).

(74) Agent: BERLINER, Robert; 707 Wilshire Boulevard, Suite 4750, Los Angeles, CA 90017 (US).

(81) Designated States: AU, CH (European patent), DE (European patent), DK, FR (European patent), GB (European patent), JP, NL (European patent), SE (European patent).

Published
With international search report
With amended claims

(54) Title: PROLONGED ACTION DRUG FORMULATION

(57) Abstract

The time during which a drug is pharmacologically active is prolonged by combining the drug with a chemical derivative of the drug having minor pharmacological activity relative to the drug.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BR	Brazil
CF	Central African Republic
CG	Congo
CH	Switzerland
CM	Cameroon
DE	Germany, Federal Republic of
DK	Denmark
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
HU	Hungary
JP	Japan
KP	Democratic People's Republic of Korea
LI	Liechtenstein
LU	Luxembourg
MC	Monaco
MG	Madagascar
MW	Malawi
NL	Netherlands
NO	Norway
RO	Romania
SE	Sweden
SN	Senegal
SU	Soviet Union
TD	Chad
TG	Togo
US	United States of America

PROLONGED ACTION DRUG FORMULATION

Background and Summary of the Invention

Medical science has long recognized the desirability of prolonging the time during which a drug is pharmacologically active. A significant advantage is to decrease the frequency with which the patient has to take the drug or be given the drug. This is particularly important when patient compliance problems are encountered such as psychiatric patients or with the senile. Extending the pharmacological activity of the drug can have significant therapeutic benefits, for example, by permitting a patient to sleep undisturbed throughout the night. Perhaps most significantly, the patient is exposed to less total active drug during any given period of time, minimizing or eliminating local and systemic side effects. Prolonged action drug formulations have utility in veterinary medicine, particularly in the treatment of free-ranging animals.

A variety of methods have been devised in an attempt to increase drug release time, including oral, parenteral and topical application techniques. For example, drugs have been encapsulated in polymer or in slowly-dissolving coating material, or have been dispersed in an insoluble or slowly-dissolving matrix. Prolonged activity formulations designed for subcutaneous and intramuscular injection have been prepared by using polymers to complex

or absorb the drug molecules in solution. Other techniques include suspension of polymer particles into which the drug is dispersed, suspension of microcapsules of the drug, use of solutions or suspensions of the drug in oil, or emulsions with oil, and implanting various slow release devices or pellets. These and other methods for providing prolonged activity are described in "Sustained and Controlled Release Drug Delivery Systems" by J. R. Robinson, Marcel Dekker, Inc., New York, 1978 (Volume 6 of "Drugs and the Pharmaceutical Sciences Series", edited by J. Swarbrick).

Most pertinent to the present development are the methods described by Anthony A. Sinkula in Chapter 6 of the foregoing test relating to the chemical approach to sustained drug delivery; that Chapter 6 is incorporated herein by reference. Such methods are based on localization of the drug in a biological depot or site within the organism with slow release to provide the active form of the drug over an extended length of time. The author describes preparation of chemical derivatives of a wide variety of drugs to increase the sustained release property of the drug molecule. In many cases, the parent molecule is regenerated in vivo by a hydrolytic mechanism. While the chemical approach would seem to offer hope for a wide variety of custom tailored prolonged action drugs, when the derivative is formulated so as to provide a significant level of drug delivery, there are a number of drawbacks pointed out by Sinkula. For example, the resulting changes in the physicochemical properties of the modified drug may well produce pharmacological and biochemical changes different from those found in the parent drug molecule. The predictability of these changes is difficult to assess, and frequently it is not possible to alter only one property of the drug. It will be appreciated that the foregoing problems arise as a result of attempting to

provide a modified drug at a concentration level having substantial pharmacological activity.

The present invention provides a prolonged action drug formulation in which a chemical derivative of the desired drug is utilized. However, in the present invention as compared to the prior use of drug derivatives, the concentration of the drug derivative is such as to provide only minor pharmacological activity. Rather than simply relying upon regeneration of the drug by decomposition of the derivative, in the present invention, for an extended period of time the derivative retains its identity, but in combination with desired quantities of the drug itself, serving by such combination to impede the release of the drug. Succinctly, the desired drug is dispersed in a suitable chemical derivative which has a reduced aqueous solubility and reduced dissolution rate.

It will be appreciated that there are several advantages to the present invention. In particular, since the pharmacological activity of the modified drug is minor relative to the activity of the drug with which it is in combination, there is little likelihood of pharmacological and biochemical changes in the derivative; there is thus a cost savings through reduced toxicity testing and dosage development time. The relationship between drug release and concentration in the combination can be readily determined and customized for any particular application by simple changes in concentration and/or the manner by which the drug and derivative are placed in combination. In contrast to some prior art vehicles which are not biodegradable, the derivative will eventually break down and be removed undergoing a reaction such as hydrolysis to reform the original drug.

More particularly, the prolonged action drug formulation of the present invention comprises, in combination, a pharmacologically effective amount of a drug in solid form and a solid chemical derivative of the drug in a concentration which is sufficient to substantially prolong the time during which the drug is pharmacologically active but having at that concentration only minor pharmacological activity relative to the drug. The combination is preferably a substantially intimate and uniform mixture, for example obtained by physical admixture followed by compaction and comminution, or by coprecipitation from a common solution, or the drug and derivative can be melted together to form a fused solid; alternatively, the derivative can be coated onto, or otherwise encapsulate, particles of the drug. The combination has particular usefulness when administered subcutaneously or intramuscularly.

The aqueous solubility (in pH 7 phosphate buffered solution) of the derivative should be less than 0.20 mg./ml., preferably less than 0.01 mg./ml. Depending upon the particular derivative and parent drug, the drug will generally constitute about 25-95 weight percent of the combination.

The prior art has used a variety of terms to characterize long-acting formulations. While one could draw distinctions between phrases such as "sustained action", "controlled release", "delayed release" and the like, as a practical matter, these terms can be used somewhat interchangeably. In this specification, the term "prolonged action" will be used to indicate all long-acting formulations, that is, formulations that have pharmacokinetic characteristics such that the formulation provides an extended length of release time than is normally found for the released drug itself.

Detailed Description

It will be appreciated that the underlying concept of the present invention has applicability to a wide variety of drugs. In particular, one could utilize as the chemical derivative component a pharmacologically appropriate derivative of the following drugs that are amenable to chemical modification: steroids, neuroleptics, beta-lactam antibiotics, antileprotics, antimalarials, hypoglycemics, narcotics and narcotic antagonists.

The main invention is exemplified with reference to the antileprotic drug diaminodiphenyl sulfone, commonly known as dapsone. This is the drug of choice in the treatment of leprosy, having strong pharmacological activity against the bacillus Mycobacterium leprae. Typical dosage is 50-100 milligrams per day for a period of five years or longer. Because of the chronic nature of this disease, a variety of derivative repository drugs have been proposed as substitutes for dapsone. These are described by Sinkula, supra, with optimum depot activity obtained with the diacetyl derivative of dapsone, 4', 4'''-sulfonyl-bisacetanilide, commonly known as acedapsone. Acedapsone is reported by Sinkula as having an aqueous solubility (pH 7 phosphate buffered solution) of 0.003 mg./ml.

When used as a "prodrug", i.e., a compound which is biotransformed into its pharmacologically active form, sufficient amount of the derivative must be used to provide the required dosage amount of the parent drug. In accordance with the present invention by combining acedapsone with dapsone, the acedapsone serves not as the source of the dapsone but physically as a matrix or coating to control the release of the dapsone with which it is present in combination. In such context, the required amount of acedapsone is much lower than when it is used as a prodrug. At the concentration used in combination with dapsone, the

acedapsone has only minor pharmacological activity relative to the dapsone component.

Other suitable parent drug-derivative combinations can be provided. For example: the steroid drug testosterone can be combined with the derivative testosterone cypionate; the neuroleptic drug fluphenazine can be combined with the derivative fluphenazine decanoate; the beta-lactam antiobiotic drug benzylpenicillin can be combined with the derivative benzathine penicillin G; the antimalarial drug cycloguanil can be combined with the derivative cycloguanil pamoate; the hypoglycemic drug insulin can be combined with the alkanedioic acid derivative of insulin; the analgesic propoxythene can be combined with the derivative propoxythene napsylate; and the narcotic antagonist naloxone can be combined with the derivative naloxone napsylate.

Further examples can be constructed by considering the aqueous solubility of various drug derivatives. In general, derivatives that are more soluble than 0.20 mg./ml. show little depot activity and therefore would be of little interest for the present combinations. Compounds of solubility below 0.20 mg./ml., preferably 0.01 mg./ml. or lower, are suitable candidates. Experimentally, one could determine the pharmacological activity of the derivative candidate and of the drug and combinations thereof to generate a simple concentration relationship so that a particular formulation can be customized.

The components should preferably be intimately and uniformly dispersed which can be accomplished by compaction of a simple admixture and comminution. As an alternative to physical admixture, one can obtain a substantially intimate and uniform combination by coprecipitation of the drug with the derivative. For example, one can dissolve the drug and the derivative in a suitable

solvent. The coprecipitate is prepared by either removing the solvent in vacuo or adding a liquid miscible with the solvent but in which both drug and the derivative have only a low solubility.

Another method of combining the components is to melt the combination to form a fused solid upon cooling.

The combination can be used in accordance with any procedure in which the drug or prodrug has been used. For example, it can be suspended in aqueous solution or in oil, as appropriate, and injected as a suspension. Alternatively, the material can be implanted in the form of a pellet or as a thin wafer, or injected as microcapsules. Because a substantially smaller amount of the derivative is used in the present context than as a prodrug, one can stay within reasonable bounds of injection volume, for example 2 ml or less for subcutaneous injection and 5 ml or less for intramuscular injection.

The following examples will further illustrate the invention.

EXAMPLE I

One can combine 0.5 grams of diaminodiphenyl sulphone (dapsone) with 0.5 grams of 4',4'''-sulfonylbiacetanilide (acedapsone) by physical admixture using a morter and pestle. The mixture is then compressed and broken down to particles of a size that can be readily injected. The resulting mixture is suspended in 3 ml of water for injection to serve as a subcutaneous or intramuscular injection. A person suffering from leprosy is given an intramuscular injection of 3 ml (containing 1 gram of the combination), the injection being repeated only once per month.

EXAMPLE II

The procedure of Example I is repeated except that the combination is obtained by coprecipitation of the dapsone and acedapsone from common solution. In this regard, one can dissolve both dapsone and acedapsone in the minimum amount of the solvent dimethylformamide. A coprecipitate is formed on the addition of an excess of water, separated by filtration and subsequently dried. The resultant combination is treated as in Example I.

EXAMPLE III

A combination is obtained by physically admixing in a mortar and pestle 0.5 grams of dapsone and 0.5 grams of acedapsone. The combination is compressed in a suitable punch and die assembly to a pellet weighing 1.0 grams each. The pellets are then implanted subcutaneously, the wound being sutured for complete enclosure of the implant. Because of the biodegradable nature of the component, no subsequent recovery of the implant is required.

EXAMPLES IV - X

The precedure of Example I can be repeated but substituting the following amounts of the listed drug and derivative:

Ex.No.	Drug	Amount	Derivative	Amount
IV	testosterone	50mg.	testosterone cypionate	150mg.
V	fluphenazine	95mg.	fluphenazine decanoate	5mg.
VI	benzylpencillin	800mg.	benazthine pencillin G	200mg.
VII	cycloguanil	200mg.	cycloguanil pamoate	100mg.
VIII	insulin	4mg.	alkanedioic acid derivative	2mg.
IX	propoxythene	30mg.	propoxythene napsylate	10mg.
X	naloxone	0.4mg.	naloxone napsylate	0.2mg.

It will be appreciated that the above listing of drugs and derivatives is not intended to be comprehensive, but merely representative of the wide variety of drugs and derivatives which can be used to constitute a combination of this invention. Those skilled in the art will know or will be able to determine by routine experimentation the many other specific drugs and derivatives that are also suitable.

THE CLAIMS

1. A prolonged action drug formulation comprising, in combination:

a pharmacologically effective amount of a drug in solid form; and

a solid cnemical derivative of said drug in a concentration which is sufficient to substantially prolong the time during which said drug is pharmacologically active and having at said concentration minor pharmacological activity relative to said drug.

2. The formulation of claim 1 in which said combination comprises a substantially intimate and uniform admixture of said drug and said derivative as a matrix.

3. The formulation of claim 1 in which said combination is a solid obtain by fusion.

4. The formulation of claim 1 in which said drug and derivative combination is obtained by coprecipitation from a common solution thereof.

5. The formulation of claim 1 in which said derivative is coated onto particles of said drug.

6. The formulation of any one of claims 1-5 in which the aqueous solubility of said derivative is less than 0.20 mg./ml.

7. The formulation of claim 6 in which the aqueous solubility of said derivative is less than 0.01 mg./ml.

8. The formulation of claim 6 in which said drug constitutes about 25-95 weight percent of said combination.

9. The formulation of any one of claims 1-5 in which said drug is diaminodiphenyl sulfone and said derivative is 4',4'''-sulfonylbisacetanilide.

10. A prolonged action drug formulation comprising diaminodiphenyl sulfone in combination with 4',4'''-sulfonylbisacetanilide, said diaminodiphenyl sulfone constituting about 25-95 weight percent of said combination.

11. The formulation of claim 10 in which said diaminodiphenyl sulfone constitutes at least 50% of said combination.

12. In a method for subcutaneously or intramuscularly administering pharmacologically effective amounts of drug in solid form, the improvement according to which said drug is placed in combination with a solid chemical derivative of said drug in a concentration sufficient to substantially prolong the time during which said drug is pharmacologically active and having at said concentration minor pharmacological activity relative to said drug.

13. The improvement of claim 12 in which said derivative is substantially intimately and uniformly admixed with said drug to form a matrix.

14. The improvement of claim 12 in which said drug and derivative are melted together to form a fused solid.

15. The improvement of claim 13 in which said drug and derivative are coprecipitated from a common solution to form said admixture.

16. The improvement of claim 12 in which said combination is obtained by coating said derivative onto particles of said drug.

17. The improvement of any one of claims 12-16 in which the aqueous solubility of said derivative is less than 0.20 mg./ml.

18. The improvement of claim 17 in which the aqueous solubility of said derivative is less than 0.01 mg./ml.

19. The improvement of claim 17 in which said drug constitutes about 25-95 weight percent of said combination.

20. The improvement of any one of claims 12-16 in which said drug is diaminodiphenyl sulfone and said derivative is 4',4'''-sulfonylbisacetanilide.

21. In a method for subcutaneously or intramuscularly administering pharmacologically effective amounts of diaminodiphenyl sulfone, the improvement whereby to prolong the time during said diaminodiphenyl sulfone is pharmacologically active, comprising combining said diaminodiphenyl sulfone with 4',4'''-sulfonylbisacetanilide so as to constitute said diaminodiphenyl sulfone about 25-95 weight percent of the resultant combination.

22.The improvement of claim 21 in which said diaminodiphenyl sulfone constitutes at least 50% of said combination.

AMENDED CLAIMS
(received by the International Bureau on 4 September 1981 (04.09.81)

1. A prolonged action drug formulated for intramuscular or subcutaneous administration, comprising, in combination:

a pharmacologically effective amount of a drug in solid form; and

a solid chemical derivative of said drug having an aqueous solubility of less than 0.20 mg./ml. in a concentration which is sufficient to substantially prolong the time during which said drug is pharmacologically active and having at said concentration minor pharmacological activity relative to said drug.

2. The formulation of claim 1 in which said combination comprises a substantially intimate and uniform admixture of said drug and said derivative as a matrix.

3. The formulation of claim 1 in which said combination is a solid obtained by fusion.

4. The formulation of claim 1 in which said drug and derivative combination is obtained by coprecipitation from a common solution thereof.

5. The formulation of claim 1 in which said derivative is a coating on particles of said drug.

6. The formulation of any one of claims 1-5 in which the aqueous solubility of said derivative is less than 0.01 mg./ml.

7. The formulation of any one of claims 1-5 in which said drug constitutes about 25-95 weight percent of said combination.

8. The formulation of any one of claims 1-5 in which said drug is diaminodiphenyl sulfone and said derivative is 4',4'''-sulfonylbisacetanilide.

9. A prolonged action drug formulation comprising diaminodiphenyl sulfone in combination with 4',4'''-sulfonylbisacetanilide, said diaminodiphenyl sulfone constituting about 25-95 weight percent of said combination.

10. The formulation of claim 9 in which said diaminodiphenyl sulfone constitutes at least 50% of said combination.

11. In a method for subcutaneously or intramuscularly administering pharmacologically effective amounts of drug in solid form, the improvement according to which said drug is placed in combination with a solid chemical derivative of said drug in a concentration sufficient to substantially prolong the time during which said drug is pharmacologically active and having at said concentration minor pharmacological activity relative to said drug.

12. The improvement of claim 11 in which said derivative is substantially intimately and uniformly admixed with said drug to form a matrix.

13. The improvement of claim 11 in which said drug and derivative are melted together to form a fused solid.

14. The improvement of claim 12 in which said drug and derivative are coprecipitated from a common solution to form said admixture.

15. The improvement of claim 11 in which said derivative is in the form of a coating on particles of said drug.

16. The improvement of any one of claims 11-15 in which the aqueous solubility of said derivative is less than 0.20 mg./ml.

17. The improvement of claim 16 in which the aqueous solubility of said derivative is less than 0.01 mg./ml.

18. The improvement of claim 16 in which said drug constitutes about 25-95 weight percent of said combination.

19. The improvement of any one of claims 11-15 in which said drug is diaminodiphenyl sulfone and said derivative is 4',4'''-sulfonylbisacetanilide.

20. In a method for subcutaneously or intramuscularly administering pharmacologically effective amounts of diaminodiphenyl sulfone, the improvement whereby to prolong the time during which said diaminodiphenyl sulfone is pharmacologically active, comprising combining said diaminodiphenyl sulfone with 4',4'''-sulfonylbisacetanilide so as to constitute said diaminodiphenyl sulfone about 25-95 weight percent of the resultant combination.

21. The improvement of claim 20 in which said diaminodiphenyl sulfone constitutes at least 50% of said combination.

EDITORIAL NOTE

The applicant failed to renumber the amended claims in accordance with Section 205 of the Administrative Instructions.

In the absence of any specific indication from the applicant as to the correspondence between original and amended claims, these claims are published as filed and as amended.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US81/00520

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[3] A61K 31/165
U.S. Cl. 424/324

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US	424/324 424/337

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	N DRUGS AND PHARM. SCIENCES, Chapter 6, Vol. 6 (1978) pp. 411-548	1-22

* Special categories of cited documents: [15]

"A" document defining the general state of the art

"E" earlier document but published on or after the international filing date

"L" document cited for special reason other than those referred to in the other categories

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
07 July 1981	13 AUG 1981
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	[illegible]

Form PCT/ISA/210 (second sheet) (October 1977)

Group Art Unit 125